

## —Report on Experiments and Clinical Cases—

## Hemorrhagic Gastric Carcinoma in an Acromegalic Patient

Hirokazu Hasegawa<sup>1</sup>, Masahiko Onda<sup>1</sup>, Norio Matsukura<sup>1</sup>, Zenya Naito<sup>2</sup>,  
Hiroshi Maruyama<sup>1</sup> and Akira Tokunaga<sup>1</sup>

<sup>1</sup>First Department of Surgery and <sup>2</sup>Second Department of Pathology, Nippon Medical School, Tokyo.

## Abstract

A rare case of hemorrhagic gastric carcinoma in an acromegalic patient is reported. A 79-year-old Japanese man was referred to our hospital with diagnoses of upper gastrointestinal hemorrhage and angina pectoris. This patient showed typical clinical features of acromegaly, with increased serum growth hormone (GH) and insulin-like growth factor I (IGF-I) level. A high titer of serum anti-*Helicobacter pylori* (*H. pylori*) IgG was also observed. After percutaneous transluminal coronary angioplasty treatment for stenosis of the right coronary artery, the patient underwent distal gastrectomy. Gastric cancer was Type 2 macroscopically and was diagnosed histologically as a papillary and well to moderately differentiated tubular adenocarcinoma. Reverse transcription-polymerase chain reaction analysis estimated that the amount of IGF-I receptor mRNA expression in the gastric cancer tissue was 1.6 times higher than that in the adjacent atrophic mucosa, whereas the amount of IGF-I mRNA expression in the cancer tissue was only half that in the atrophic mucosa. Both the stimulatory effects of GH and/or IGF-I on cell proliferation and *H. pylori* infection in gastric tumorigenesis may have been responsible for the development and growth of gastric carcinoma in this patient. (J Nippon Med Sch 2001; 68: 266–270)

**Key words:** acromegaly, gastric cancer, growth hormone, insulin-like growth factor I, *Helicobacter pylori*

## Introduction

Acromegaly is a chronic adult disease characterized by progressive enlargement of peripheral parts of the body due to excessive secretion of growth hormone (GH) and insulin-like growth factor I (IGF-I), usually occurring as a result of a somatotroph pituitary adenoma. Many of the growth-promoting actions of GH on tissue are not exerted directly but rather are mediated by IGF-I. Serum IGF-I is mainly produced by the liver and also by a wide variety of cell types, including fibroblasts, smooth muscle cells, endothelial cells, and several cancer cells<sup>1</sup>. The expression of IGF-I receptor, a membrane glycoprotein and a member of

the tyrosine-kinase receptor family, has also been studied in several malignancies<sup>2</sup>. Gastrointestinal neoplasms in acromegalic patients seem to occur with greater than the expected incidence. An increased incidence of stomach cancer has been suggested in a few published retrospective studies<sup>3,4</sup>, but neither the prevalence rate of stomach cancer nor the mechanisms of gastric carcinogenesis have been clarified in these reports. We experienced a rare case of hemorrhagic gastric carcinoma in an acromegalic patient with angina pectoris. The expression of both IGF-I and its receptor mRNAs in the carcinoma tissue was examined and compared with those in the adjacent nonmalignant atrophic mucosa. The possible roles of GH and/or IGF-I and *Helicobacter pylori* (*H. pylori*) in-

Corresponding to Hirokazu Hasegawa, MD, First Department of Surgery, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan

E-mail: kazunn@nms.ac.jp

Journal Website (<http://www.nms.ac.jp/jnms/>)

Table 1 Results of Serum Endocrinological Examinations on Admission

Growth hormone (GH)	8.8 ng/ml	(< 5)
Insulin like growth factor- I (IGF- I )	590 ng/ml	(106 – 398)
Follicle stimulating hormone (FSH)	33.7 mIU/ml	(1 – 11)
Prolactin (PRL)	31.6 ng/ml	(2 – 17)
Adrenocorticotropin (ACTH)	18 pg/ml	(9 – 52)
Thyroid stimulating hormone (TSH)	0.05 $\mu$ U/ml	(< 5)
Luteinizing hormone (LH)	3.5 mIU/ml	(2 – 6)
Gastrin	318 pg/ml	(< 200)
(Normal range in parenthesis)		
Serum GH level (ng/ml)		
	0 min	30 min
	60 min	90 min
	120 min	180 min
Oral administration of 75g glucose	9.6	13.6
	14.6	15.4
	14.0	16.3

fection in the development and growth of gastric carcinoma are discussed.

### Case Report

A 79-year-old Japanese man was referred to our hospital with diagnoses of upper gastrointestinal hemorrhage and angina pectoris in July of 1998. His wife had been aware of a gradual increase in the size of the nose, lips, nasolabial skin folds and forehead as well as increased extremity size over a period of 10 years. Five years before the present admission he was found to have colon polyps and several endoscopic polypectomies had been done elsewhere.

On admission, typical physical features of acromegaly were noted and he had severe hypochromic anemia due to melena with a hemoglobin level of 5.7 g/dl, red blood cell count of  $283 \times 10^4/\text{mm}^3$  and hematocrit of 18.4%. Other routine laboratory examinations disclosed elevations of blood urea nitrogen (33.2 mg/dl), creatinine (2.2 mg/dl) and creatine phosphokinase (339 IU/l) values. The fasting blood sugar concentration was 98 mg/dl. An elevated carcinoembryonic antigen (CEA) value (12.0 ng/ml; normal range, <2.5 ng/ml) and a high titer of serum anti-*H. pylori* IgG (186 U/ml; normal range, <30 U/ml) were revealed. The results of endocrinological examinations are summarized in **Table 1**. Plasma GH, IGF-1, follicle stimulating hormone, prolactin, and gastrin levels were high. Oral administration of 75 g glucose paradoxically increased the serum GH level. X-ray and computerized tomographic (CT) scans identified a large pituitary tu-

mor (**Fig. 1, 2**). Upper gastrointestinal endoscopy revealed a hemorrhagic Type 2 gastric cancer, which appeared as an ulcerated carcinoma with sharply demarcated and raised margins<sup>5</sup>. Gastric biopsy revealed a tubular adenocarcinoma. Pre-operative examinations, including abdominal and neck CT scans, revealed no evidence of liver metastasis, tumor gastrinoma or any endocrine neoplasms. From these findings, we diagnosed this patient as having a gastric carcinoma with acromegaly.

Two weeks after percutaneous transluminal coronary angioplasty treatment for stenosis of the right coronary artery, the patient underwent distal gastrec-



Fig. 1 A standard lateral radiograph of the skull reveals gross alterations of the sella turcica profile.

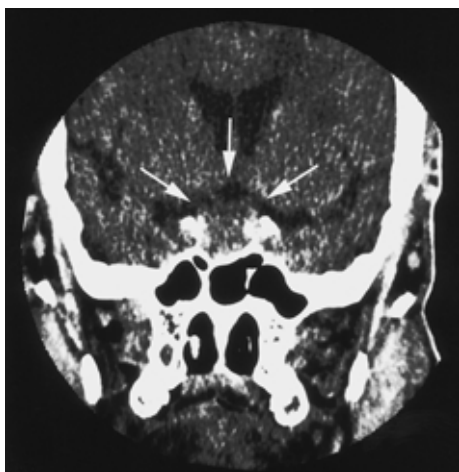


Fig. 2 A computerized tomogram of the pituitary fossa shows suprasellar extension of the pituitary tumor.



Fig. 3 Macroscopic picture of the resected stomach revealing a Type 2 gastric cancer, measuring 9 cm in diameter.

tomy with D 2 lymphadenectomy<sup>5</sup> in August 1998. A Type 2 gastric cancer was recognized on the posterior wall of the gastric angulus-antrum (**Fig. 3**). Microscopic examination revealed that the lesion, surrounded by chronic metaplastic atrophic mucosa, was a papillary and well to moderately differentiated tubular adenocarcinoma invading to the serosal surface of the stomach (**Fig. 4**) and metastasis was seen in several perigastric lymph nodes. Immunohistochemically, the tumor cells were positive for CEA but negative for IGF-I, estrogen receptor, and chromogranin A.

Furthermore, the expressions of IGF-I, IGF-I receptor and  $\beta$ -actin mRNAs in the gastric carcinoma and adjacent atrophic mucosa specimens were examined by reverse transcription-polymerase chain reaction (RT-PCR) analysis. Parts of the IGF-I gene<sup>6</sup>, IGF-I receptor gene<sup>7</sup> and  $\beta$ -actin gene<sup>8</sup>, as an internal control,

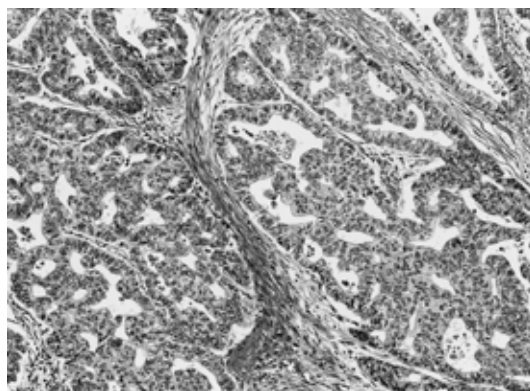


Fig. 4 Microscopic examination of the resected gastric cancer reveals the lesion to be a papillary and well to moderately differentiated tubular adenocarcinoma. (Hematoxylin and eosin,  $\times 50$ ).

were amplified and analyzed. Southern hybridization and quantitative comparison of the hybridization signal were carried out as described previously<sup>8</sup>. Expression proportions of IGF-I mRNA for  $\beta$ -actin mRNA in the carcinoma tissue and the atrophic mucosa were 0.60 and 0.32, respectively, and those of the IGF-I receptor mRNA were 0.84 and 1.31, respectively (**Fig. 5**).

The postoperative course was uneventful thereafter. A fall in CEA value was found ( $<0.5$  ng/ml) after the operation but GH, IGF-1, follicle stimulating hormone and prolactin levels remained high. He has developed no clinical manifestations due to gastric carcinoma recurrence to date, two years after the operation. The patient has refused any further treatment for either the gastric carcinoma or the acromegaly.

## Discussion

Acromegaly, afflicting men and women equally, is an uncommon disease and a slowly progressive condition resulting from unrestrained secretion of GH and IGF-I. The annual incidence is about 3.0~3.3 per million, the prevalence about 40~70 per million<sup>9,10</sup>. Though malignancy is among the important factors contributing to the increased mortality rate of acromegalic patients, there is no convincing epidemiological evidence of an association between acromegaly and gastric cancer because gastric cancer with acromegaly is very rare. A cohort, consisting of 1,041 men with a diagnosis of acromegaly in the

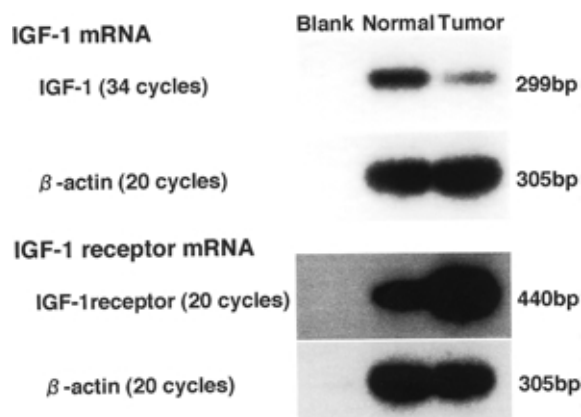


Fig. 5 RT-PCR amplification of IGF-I, IGF-I receptor and  $\beta$ -actin mRNAs using total RNA extracted from the gastric cancer and from the nonmalignant atrophic mucosa. Parts of the IGF-I gene and IGF-I receptor gene were amplified with the following primers: sense primer; 5'-ATGCACACCATGTCCTCCTC-3' and antisense primer; 5'-GCACGGACAGAGCGA-GCTGA-3' for the IGF-I gene and sense primer; 5'-AGCCGATGTGTGAGAAGACC-3' and antisense primer; 5'-TTCTTCCTCACAGAC-CTTCG-3' for the IGF-I receptor gene. The sequences of probes were as follows: IGF-I, 5'-GCTGGTGGATGCTCTTCAGTTCGTGTGTGG-3'; IGF-I receptor, 5'-CCACTACTACT-ATGCCGGTGTCTGTGTGCC-3'. The results of Southern analysis for PCR products are shown. bp, base pairs.

United States, was examined for subsequent cancer and stomach cancer was recognized in four cases (0.38%)<sup>3</sup>. Only ten cases, including our case, have been reported since 1983 in Japan<sup>4</sup> and the putative mean incidence of gastric cancer among acromegalic patients is about 3.3 times higher than the overall incidence of gastric cancer. It is noteworthy that there were 6 men and 4 women and that 4 of 5 cases of advanced gastric cancer were Type 2, and 4 of 5 cases of early gastric cancer were Type 0 IIc or Type 0 IIc+III<sup>5</sup>.

There is a pathological association between atrophic gastritis and gastric carcinoma *via* intestinal metaplasia<sup>11</sup>. Epidemiological and experimental evidence suggests a link between *H. pylori* infection in the stomach and the subsequent development of gastric carcinoma<sup>11,12</sup>. In our case, the presence of *H. pylori* infection was assessed serologically. There is also considerable biological evidence concerning the association between GH or IGF-I and tumorigenesis or cell proliferation in nonacromegalic patients. RT-PCR

analysis detected both human GH and prolactin receptor transcripts in both the gastric cell fraction and in the primary gastric carcinoma<sup>13</sup>, and *in situ* hybridization and immunohistochemical analysis revealed the expression of IGF-I and IGF-I receptor mRNAs in both tumor cells of the gastric cancer and nonmalignant mucosa<sup>14</sup>. However, the reasons for the higher risk of neoplastic lesions in acromegalic patients have still not been ascertained. In our case, there was a quantitative difference in the expressions of IGF-I and IGF-I receptor mRNAs between the gastric cancer tissue and those in the adjacent atrophic mucosa. The amount of IGF-I receptor mRNA expression in the gastric cancer tissue was estimated to be about 1.6 times higher than that in the adjacent atrophic mucosa, whereas the amount of IGF-I mRNA expression in the cancer tissue was only half that in the atrophic mucosa. From these observations, we speculate that the tumor tissue may have acquired the expression of an abnormal amount of IGF-I receptor mRNA in the processes of malignant transformation. Then, GH and IGF-I, either alone or in cooperation with other hormones, would have continuously stimulated tumor growth and influenced the morphological manifestations of the tumor in an endocrine and/or autocrine/paracrine manner by interacting with their respective receptors. Further study is needed to clarify the gastric carcinogenesis associated with acromegaly.

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